

SOME NOVEL EFFECTS OF PROGES-TERONE

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Besides its usual physiological effects on the endometrium, breast and vagina, it has been found that progesterone affects the activity of myometrium and several other tissues and system, and modifies the effects of various drugs and pharmacologically active substances. These aspects of the pharmacology of progesterone are briefly reviewed here.

1. Modification of the effects of other drugs

(i) Myometrium and related tissues: On the basis of the observations that radioactive progesterone is specifically taken up by the uterus from the plasma against a concentration gradient, it has been proposed that the uterus contains specific cytoplasmic receptors for binding progesterone (Davies and Ryan, 1972). Studies on the measurement of the concentration of these receptor sites in the cytosol of the rat myometrium, have revealed that the number of receptor sites increases to a maximum of about 20 p moles/mg of protein around the 9th day of pregnancy, a decline is evident by the 12th day and the level falls to 5 p moles/mg of protein in the last week of gestation. The elevation of myometrial progesterone above that of plasma, and the subsequent disappearance of this difference is well correlated with changes in cytoplasmic progesterone receptor concentration. These observations indicate that the concentration of progesterone in the myometrium of the pregnant rat is controlled not only by plasma hormone concentration but also by changes in cytoplasmic progesterone receptor concentration, and that the occurrence of parturition is correlated better with the concentration of progesterone in the myometrium than with that in plasma (Davies and Ryan, 1973). The binding of the hormone by specific cytoplasmic receptors is an important primary event, which is followed by movement of the protein steroid complex to the nucleus where alteration of cellular function, is initiated (Davies and Ryan, 1972). Besides cytoplasm, a specific progesterone receptor has also been isolated from the nuclei of the cells after incubation of chick oviduct tissues with H³ progesterone. Within the nucleus the receptor is attached to chromatin and it has been observed that as the nuclear binding increases, binding in the cytoplasm falls (O'Malley et al., 1970 cited by King and Main Waring, 1974). Oestrogen has been reported to increase the uptake of progesterone in the oviduct of chick (Toft and O'Malley, 1972), and the uteri of rabbit (Faber et al., 1973), and hamster and guinea-pig. (Milgram, 1970 cited by Davies and Ryan, 1973), but there is no direct evidence to indicate interaction between oestrogen and rat uterine progesterone receptors (Davies and Ryan, 1973).

During pregnancy the myometrium shows refractoriness to the effect of several oxytocic drugs like histamine (Kameswaren et al., 1962), oxytocin (Knifton, 1968 cited by Abdel Aziz and Bakry, 1973). The effect has been linked with increased progesterone level during pregnancy which is responsible for the development of 'progesterone block', a condition characterized by an increase in the resting membrane potential, increase in the threshold of excitation and a greater binding capacity for calcium by myometrium (Marshall, 1959). These physiological changes are responsible for the induction of uterine quiescence which is the primary cause of the decrease in sensitivity to drugs and electrical stimuli, and also an essential requirement for the maintenance of pregnancy (Davies and Ryan, 1973). In non-ovariectomized rats, progesterone therapy decreases the sensitivity of the isolated rat uterus preparation to oxytocin, 5 hydroxy-tryptamine and acetylcholine, whereas, in ovariec-tomized rats, progesterone pretreatment increases the sensitivity of the isolated rat uterus preparation to these drugs (Khan and Ahmad, 1969).

Adrenaline, noradrenaline and isoprenaline produce an inhibitory effect on the progesterone dominated rat uterus. However, the effects of noradrenaline become excitatory when the animals are in oestrus or

are treated with stilboestrol. Oestrogen is thus believed to increase the sensitivity of alpha adrenergic receptors of uterus. Progesterone, on the other hand, produces its effects by increasing the sensitivity of inhibitory beta adrenergic receptors to various catecholamines (Tothill, 1967; Butterworth and Randall, 1970).

Studies on the effects of intravenously administered prostaglandins, PGE1, and PGF2£ on the spontaneous activity of the uterus of anaesthetized rabbits have shown that progesterone pretreatment prolongs the effects of 5 ug/kg PGE1, but antagonizes the effects of similar concentrations of PGF2£ (Spilman, 1974).

(ii) Ureter:

Raz et al (1972) have shown that, whereas, adrenaline produces an inhibitory effect on the rate of spontaneous contractions of the ureters obtained from untreated rats, it produces an increase in the rate of spontaneous contractions of the ureters obtained from the animals treated with the beta adrenergic blocking agent, inderal, but inderal is unable to modify the inhibitory effects of adrenaline when it is administered in combination with progesterone. Progesterone, according to these workers, is thus believed to increase the sensitivity of the inhibitory beta adrenergic receptors of the ureter. The mechanism of dilatation of- ureters during pregnancy and in the case of therapy with oral contraceptives has been explained on the basis of these observations (Raz et al., 1972).

(iii) Urethra.

It has been shown that progesterone treatment (50 mg daily for 8 days) causes a reversal of the stimulatory effect of isoprenaline on the urethra of the pentobarbitone anaesthetized dogs (Raz et al., 1973).

(iv) Cardiovascular system:

Oxytocin is pressor and vasoconstrictor when injected in female rats at the time of oestrus, whereas, it dilates the mesenteric vessels and produces no significant effect on blood pressure in other phases of the oestrus cycle. Vasopressin is pressor and constrictor at all times, but the pressor response to a given dose is greater at the time of oestrus than at other times. In ovariccto-mized rats, oxytocin produces no effect on blood pressure, but vasopressin always has a pressor effect. In the ovariectomized rats, though administration of progesterone alone docs not modify the effect of oxytocin on the blood pressure, combined injections of oestrogen and progesterone produce a typical response resembling that of oestrus (Llyod,1959).

Although there is no significant difference between the hypertensive responses to angiotensin in pentobarbitone anaesthetized rats in oestrus or other phases of the oestrus cycle, pregnancy depresses responses to angiotensin and similar effects have been seen in rats treated with progesterone (Hettiaratchi and Pickford, 1968). The antagonism of angiotensin may be due to an increase in the level of renin brought about by progesterone (Winer, 1965), as there is evidence to show that the sensitivity of a species to the vasoconstrictor action of exogenous angiotensin varies inversely with the level of endogenous renin and angiotensin production (Gross et al., 1965 cited by Hettiaratchi and Pickford, 1968).

In pithedfemale rats progesterone treatment (20 mg/kg for 14 days) increases the duration (but not the magnitude) of the hypertensive and cardiac stimulant effects of adrenaline, and similar effects of that phase of sympathetic stimulation which is due to the release of adrenaline from the adrenal medulla. On the other hand, responses to noradrenaline, tyramine, 5-hydroxytrypfamine and that phase of sympathetic stimulation which is associated with amine release from the sympathetic nerve endings are not affected (Fozard, 1971). It has been postulated on the basis of these observations that the effects of progesterone therapy on the hypertensive and cardiac stimulant responses of adrenaline and sympathetic stimulation may result from a decrease in the activity of the enzyme catechol-o-methyl transferase (COMT) within the cardiovascular system (Fozard, 1971). This action of progesterone may be responsible for its beneficial effect in the treatment of migraine (Singh et al, 1947; Fozard, 1971). Progesterone (when added in the isolated organ bath) prolongs the duration of responses to adrenaline,

noradrenaline and nordefrine on the isolated rabbit aortic strips. On preparations obtained from untreated and reserpine treated animals, responses to tyramine are enhanced only in the untreated group. As these typical effects of progesterone are abolished by the inhibitors of COMT, and progesterone decreases the rate at which aortic strips inactivate adrenaline by O-methylation, it has been suggested that progesterone produces these effects by inhibiting COMT and, thereby, a major mechanism for the inactivation of catecholamines (Kalsner, 1969).

Progesterone (5 mg/kg, I/M, for; fourteen days) causes depression of the contractile responses of the isolated preparations of the central ear artery of the rabbit produced by the electrical stimulation of the nerve fibres, but does not modify the responses of this preparation to noradrenaline, tyramine and histamine. On the other hand, similar progesterone therapy increases the sensitivity of this preparation to tryptamine and 5-hydroxytryptamine (Fozard and Schneiden, 1970)."

On the isolated spirally cut strips of the human and dog saphenous veins, progesterone, when applied directly, reduces the magnitude of responses produced by noradrenaline, acetylcholine and electrical stimulation without showing a relaxant effect of its own (Fogarty, 1971).

2. Other effects:

(i) Intact animals ;

Progesterone, when injected intramuscularly, abolishes auricular flutter in anaesthetized dogs (Arman and Drill, 1958). The daily administration of progesterone to dogs leads to an increase in plasma renin level. Sodium depletion, produced due to the antagonism of aldosterone by progesterone at the renal tubular level, is considered to be the possible cause of this increase in renin production (Winer, 1965). Increase in progesterone secretion is considered to be the basis for the extrauterine weight gain (due to retention of water and increase in protein and fat contents) in pregnancy and pseudopregnancy (Hervey and Hervey, 1967). The subcutaneous administration of progesterone, in 5 mg/kg doses for 7 weeks, prevents the development of experimental emphysema in rats (Ito and Aviado, 1968).

It has long been recognized that ureteral dilatation is common in pregnant women (Baird, 1933 cited by Marshall et al., 1966). Van Wagenan and Jenkins (1939) have demonstrated in monkeys that the ureteral dilatation in pregnancy is not due to the mechanical pressure exerted by gravid uterus, but is produced by the placental hormones. Marshall et al (1966) have reported the development of ureteral dilatation during the use of an oral contraceptive, an effect which disappears after the drug is stopped. It is believed that progesterone plays a prominent role in the development of dilatation of ureter and the accompanied decrease in its peristaltic activity (Raz et al., 1972).

(ii) Isolated Preparations;

Progesterone has been reported to produce digitalis like effects on the isolated perfused frog heart (Hajdu, 1957), whereas, it decreases the activity of isolated perfused rabbit heart, when injected into the perfusion fluid (Arman and Drill, 1958). In the isolated perfused rat heart, the addition of progesterone to perfusion fluid produces a concentration dependent inhibition of the uptake of H³ noradrenaline by the uptake-2 (i.e. uptake by the smooth muscle cells) mechanism (Iverson and Salt, 1970).

Progesterone produces a gradual decline in the contractility of the electrically driven isolated guinea pig ventricular muscle strip preparations; this effect is produced when the temperature of the nutrient solution is 37°C, but cannot be obtained at 24°C. Progesterone produces these effects by causing a reduction in the uptake of calcium ions by the cells (Mendoza and DeMello, 1974).

Progesterone induces a dose dependent increase in the rate and decrease in the amplitude of spontaneous contractions of the isolated rat portal vein preparation, an effect which is obtained even in the presence of beta adrenoceptive blockade with propranolol (McCalden, 1975). As similar preparations obtained from pregnant rats also show a statistically significant decrease in the amplitude of contractions, it has been suggested that decrease in the amplitude of spontaneous contractions of the veins induced by progesterone may be one of the contributing factors in the development of venous thrombosis in pregnancy (McCalden, 1975).

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